

The Pathogenesis Based on the Glymphatic System, Diagnosis, and Treatment of Idiopathic Normal Pressure Hydrocephalus

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Abstract: Idiopathic normal pressure hydrocephalus (iNPH) is a rare neurological disorder with no clear prevalence factors and is a significant danger to the elderly. The intracranial glymphatic system is the internal environment that maintains brain survival and metabolism, and thus fluid exchange changes in the glymphatic system under various pathological conditions can provide important insights into the pathogenesis and differential diagnosis of many neurodegenerative diseases such as iNPH. iNPH can be diagnosed using a combination of clinical symptoms, imaging findings and history, and cerebrospinal fluid biomarkers due to the glymphatic system disorder. However, only few researchers have linked the two. Shunt surgery can improve the glymphatic system disorders in iNPH patients, and the surgical approach is determined using a combination of clinical diagnosis and trials. Therefore, we have composed this review to provide a future opportunity for elucidating the pathogenesis of iNPH based on the glymphatic system, and link the glymphatic system to the diagnosis and treatment of iNPH. The review will provide new insights into the medical research of iNPH.

Keywords: idiopathic normal pressure hydrocephalus, glymphatic system, pathogenesis, diagnostic methods, shunt surgery

Idiopathic Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) is a treatable but difficult to diagnose neurological disorder,¹ which was first proposed by Adams et al, (1965). The patients exhibit classic a triad of symptoms including gait and balance disorders, urinary incontinence, and cognitive impairment.^{2,3}

Idiopathic normal pressure hydrocephalus (iNPH) is a kind of NPH with no clear cause, often occurring in the elderly, and imaging analysis indicates a normal cerebrospinal fluid (CSF) pressure and enlarged ventricle.³ A previous study reported that it can be relieved through early diagnosis and surgical intervention.⁴ However, it is difficult to diagnose and distinguish the disease because there is no specific cause of iNPH. Therefore, there is still some controversy over the specific classification of iNPH. In Europe and Japan, iNPH is considered as an independently diagnosed disease, whereas in the United States it is classified as a subtype of Alzheimer's disease (AD). Although the iNPH disease theoretically exhibits a triad of symptoms typified by cognitive impairment, urinary incontinence, and gait disturbance, in actual cases few patients have all three symptoms at the same

time. Once misdiagnosis occurs, the patient fails to receive effective treatment, thereby causing aggravation over time. Therefore, we can improve the diagnostic efficiency and identify potential patients with iNPH by learning about the symptoms and diagnosis of iNPH, as well as exploring more efficient assessment scales and comparative disease analysis. This may allow patients to receive appropriate treatment as early as possible.

Generally, iNPH is a relatively rare disease, mostly occurring in the elderly. Martin-Laez et al, (2016) concluded that iNPH is an aging-related disease and its prevalence will exponentially increase with age in the future.⁵ Previous studies have reported that the prevalence is about 3.7% in people above 65 years of age and 5.9% in individuals over 80 years of age, sometimes even rising to 8.9% in some regions, which is about four times the prevalence (2.1%) between 65 to 79 years of age.^{2,6,7} iNPH was first reported in 1989 at a frequency of 0.5% in the elderly people over 67 years of age.⁸ However, it was not strictly a prevalence estimate since the whole population was not screened. Subsequent studies conducted between 1986 and 2000 reported that the prevalence was 2.1% in elderly individuals over 70 years of age, while the latest study reported a prevalence rate of 3.7% in elderly people over 65 years of age, but both estimates have age limits.² Some studies have also shown that the prevalence of iNPH is not associated with gender, perhaps because of the geographical and sample differences.^{7,9} However, most of the above mentioned data has limitations, such as being applicable within a specific region or the inclusion of iNPH patients is based on surrogate information like the International Classification of Diseases diagnosis code for iNPH,¹⁰ which may result in a lower prevalence. Therefore, the prevalence of iNPH and the diagnostic guidelines still need to be further elucidated.

Shunt surgery is the most common treatment method for individuals with iNPH because it can effectively alleviate the condition of current iNPH patients.¹¹ However, the prognosis gradually deteriorates over time.¹² Since the patients are relatively older and may have several underlying diseases, taking their clinical indications into consideration may aid in improving the prognosis and their quality of life.

Glymphatic System in the Brain

CSF is primarily produced by the choroid plexus in the lateral ventricles, and then it flows through the third and fourth ventricles into the subarachnoid compartment of the

skull and spinal cord, where it is absorbed by venous blood from convex arachnoid granules. In addition, CSF is drained to the cervical lymph nodes along the olfactory nerve through the cribriform plate towards the lymphatic vessels of the nasal mucosa.¹³ The meningeal lymphatic vessels, which are located around the dural sinus, middle meningeal artery, and cribriform plate, can also drain CSF to the cervical lymph nodes.¹⁴ CSF from the subarachnoid space is driven into the perivascular spaces of the cerebral arteries on the brain surface. It then flows to the brain parenchyma through the astrocyte aquaporin (AQP) thereby forming interstitial fluid, which in turn flows into the perivascular spaces of the venules. Finally, it can be eliminated via the blood circulation. Only three subtypes of AQP (AQP1, 4, and 9) have been found in the mammalian central nervous system (CNS).¹⁵ Previous studies have reported that AQP1 is generally expressed in capillary endothelial cells, but its expression is inhibited in brain capillary endothelial cells, thereby effectively separating CSF from blood and interstitial fluid.^{16,17} On the other hand, AQP4 is expressed and polarized in the astrocyte terminals of the pericapillary spaces of the brain capillaries, and communicates with the glymphatic system circulation between CSF and interstitial fluid.^{18,19} Therefore, a portion of CSF flows into the brain parenchyma from the pericapillary Virchow-Robin Space via the AQP4 system of blood-brain barrier astrocytes, thereby forming interstitial fluid.^{20–22} This process also regulates local cerebral blood flow in accordance with the glymphatic system pressure.²¹

The previous view assumed that this was a unidirectional flow,²³ but Yamada et al, (2016) found that cerebrospinal fluid does not only flow unidirectionally from the site of generation to absorption.²⁴ This is because as it flows through the dural sheaths or lymphatics surrounding the cranial and spinal nerves and meninges, CSF is drained into the cervical lymphatics and is involved in the regulation of CSF levels, suggesting that multiple factors influence the intracranial glymphatic circulation. A previous study reported that fluid exchange changes in the glymphatic system under various pathological conditions can provide important insights into the pathogenesis and differential diagnosis of many neurodegenerative diseases, such as iNPH.²² Therefore, we have composed this review to discuss iNPH from the perspective of the glymphatic system with the overarching goal of providing new insights into the study of iNPH.

Glymphatic System and the Pathogenesis of iNPH

Studies on the fluid exchange between the ventricles, sub-arachnoid space, perivascular Virchow-Robin Space, and glymphatic system of patients with iNPH are increasing. Ringstad et al, (2018) and Eide et al, (2019) compared the efficiency of glymphatic clearance in iNPH patients with that in normal subjects by injecting contrast media.^{25,26} The obtained results indicated that the efficiency of glymphatic clearance was significantly reduced in iNPH

patients,^{25,26} suggesting that glymphatic system disorders may be one of the causes of the disease (Figure 1).²⁵⁻²⁸

Dynamic Disorders of Glymphatic System

It was previously thought that the driving force for CSF movement came from the lateral ventricular plexus, but the development of imaging techniques has led to the discovery that the lateral ventricular plexus is only part of the driving force.^{17,23} It also consists of cardiac-related ICP pulsations, which are associated with systole and

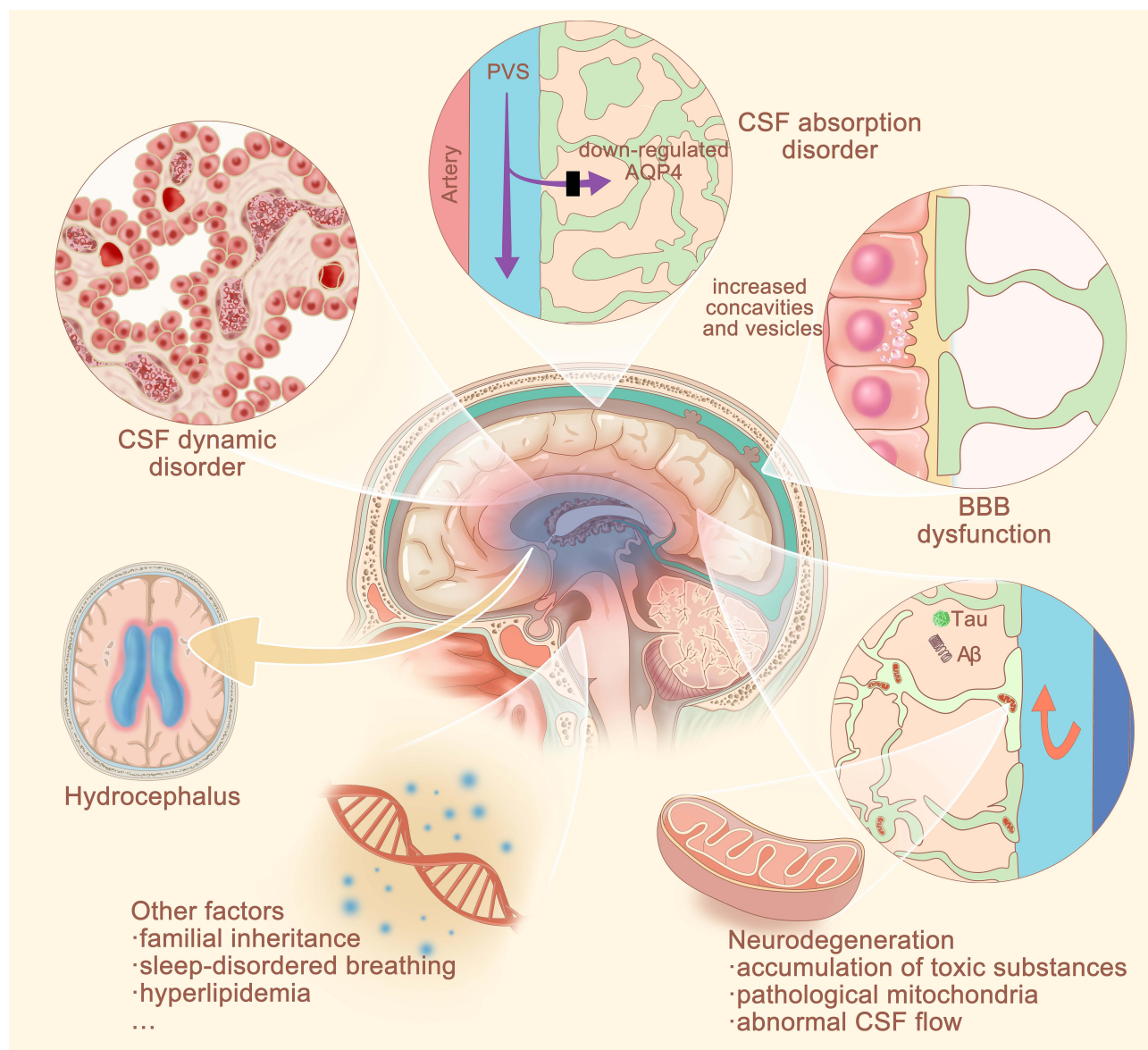


Figure 1 Pathogenesis of iNPH. Abnormalities in the choroid plexus pulses affected by heartbeat and respiratory rate, thereby leading to an impairment of CSF dynamics. Down-regulation of astrocyte terminal foot AQP4 protein, thereby leading to impaired CSF absorption. Abnormalities in the protein transport mechanism of blood-brain barrier endothelial cells, thereby leading to abnormal accumulation of proteins in the CSF. Impaired clearance and accumulation of neurotoxic substances, reduced transport efficiency of mitochondrial lesions, and abnormal flow of CSF, all resulting in neurodegenerative lesions. Other genetic, sleep apnea and hyperlipidemia factors may also be associated with the pathogenesis of iNPH.

Abbreviations: AQP, aquaporin; CSF, cerebrospinal fluid; iNPH, idiopathic normal pressure hydrocephalus.

diastole of the heart.¹⁷ Schley et al, (2006) set up a theoretical model which demonstrated that the motive force is related to the pulse wave travelling along the arteries, and that a decrease in the pulse wave impedes glymphatic drainage within the brain.²⁹ Several studies have reported that restricted cardiac activity leads to restricted arterial pulsations and decreased glymphatic flow, thereby resulting in disturbed CSF pulsation patterns and altered cerebral perfusion.^{22,27,30,31} Familiarly, respiratory-related ICP pulsations increases intracranial volume, decreases intracranial compliance, pressurizes cortical veins, and increases intraventricular pressure,³² which in turn leads to an imbalance of CSF production and absorption.^{33–35} In addition, respiratory and pathological intracranial pressure pulsations cause abnormal CSF flow and intracranial CSF redistribution.³⁶ Previous related studies have found that the spinal CSF may be formed to buffer the increased demand for CSF flow through the lymphatic system during deep inspiration to compensate for venous outflow.³⁶ Among them, the increase of CSF in the ventricles leads to its excessive accumulation in the suprasellar cistern, which may cause enlargement of the ventricles and put more pressure on the cortex. The ventricles would be further enlarged when the pressure exceeds the upper limit of cortical elastic tension, thereby causing the ICP to return to normal.³

Absorption Disorders of the Glymphatic System

The glymphatic system is absorbed into the peripheral veins of the brain, mainly through arachnoid granules. Generally, the blood-brain barrier, composed of tightly connected capillary endothelial cells in the brain, separates CSF from blood and restricts the exchange of macromolecules to maintain the osmotic pressure of CSF.

The main mediators connecting the CSF to the blood circulation are the AQP4 of the astrocytes surrounding the intracranial capillaries. Previous studies have found that iNPH patients have a decreased astrocyte AQP4 expression.^{37,38} This can interfere with the homeostasis of the glymphatic system in the brain, or cause an imbalance in the supply and demand of CSF in the cortical capillaries and local subarachnoid space, thereby resulting in super-posterior displacement of brain tissues, which in turn leads to local ischemia.³⁹ It is worth noting that the local ischemia is accompanied by disturbed neuronal metabolism and accumulation of neurotoxic substances in

the glymphatics.^{16,40} A previous study reported that the accumulation of neurotoxic substances interferes with the stability of CSF perfusion.³⁰ Furthermore, cerebral ischemia occurs concurrently with hypoxia, which leads to significant changes in the extracellular matrix composition, endosomal lysosomal systems, and mitochondrial energy metabolic capacity.⁴¹ This results in an imbalance in the supply of ions and metabolites, and abnormal circulation in the glymphatic system of the brain, ultimately leading to neurodegeneration.³⁰

For example, deletion of the AQP4 gene decreases the clearance of cerebral interstitial fluid through the periventricular Virchow-Robin Space drainage pathway by approximately 70%, thereby leading to abnormal CSF flow and intermediate metabolite disruption, which ultimately leads to slow neurodegeneration.³⁷ Moreover, the mitochondria-endoplasmic reticulum contact sites regulate the metabolism of soluble amyloid β (A β), whose number is positively correlated with age in iNPH patients.⁴² Hasan-Olive et al, (2019) found pathological mitochondria in patients,⁴³ whose presence may also contribute to the deposition of soluble A β and cause mental disorders in iNPH patients. In addition to impaired uptake by the glymphatic system, several other studies have found that patients with iNPH also partially exhibit reduced corticospinal excitability and reduced intracortical inhibitory connections in frontal and primary motor areas.^{44–46} This finding suggests that neurotransmitters such as γ -aminobutyric acid and cholinergic neurotransmitters are also affected.^{44–46}

In addition to the AQP4 system, both blood-brain barrier protein leakage and impaired circulation of CSF may lead to abnormal impairment of glymphatic metabolism, thereby causing sub-ischemia which ultimately leads to glial hyperplasia and neuronal degeneration,⁴⁷ exhibiting possible manifestations of iNPH. Ueno et al, (2006) examined blood-brain barrier permeability in a mice model of neural cell-specific hypoxia-inducible factor-1 α -deficient-induced hydrocephalus.⁴⁸ They found no significant difference between the mice model and the controls, suggesting that spontaneous hydrocephalus may not, in turn, significantly affect the blood-brain barrier.⁴⁸ In a study of tissue biopsies obtained from iNPH patients, Andreone et al, (2017) reported that the patients did not have severe damage to the small blood vessels in the brain, but rather an increase in vesicles in the luminal side of the capillary endothelial cell lumen and in the cytoplasm.⁴⁹ The vesicles are loaded with blood proteins including

fibronectin (pro), which play a transmembrane role, and thus their abnormal increase can lead to leakage of blood proteins.⁴⁹ Another study reported that large amounts of CSF entering the bloodstream also appear to pass through the large vesicles formed on the luminal surface of endothelial cells, where they discharge their contents into the venous bloodstream.⁵⁰ Hasan-Olive et al, (2019) also found that the presence of pathological mitochondria in perivascular astrocytes in patients' cerebral vessels severely affects transmembrane protein transport.⁴³ The dysfunction of neurovascular units in the blood-brain barrier may also lead to neurodegenerative changes characterized by iNPH, failure of para-vascular clearance, and CSF circulation disorders.⁵¹

Satow et al, (2017) reported that cerebral deep vein dysfunction in iNPH patients leads to a difference in drainage capacity between the superficial and deep venous systems, which in turn results in a transmembrane pressure in the brain parenchyma glymphatic system that accelerates the disease process.⁵² In addition, basement membrane and pericytes also maintain the stability of the blood-brain barrier, suggesting that they are also involved in the development of hydrocephalus to some extent.^{53,54}

Glymphatic System and Diagnosis of iNPH

iNPH is a chronic disease that undergoes different factors leading to ventricular dilation and white matter lesions, thereby creating a vicious circle that further produces a triad of symptoms typified by cognitive impairment, urinary incontinence, and gait disturbance. According to international and Japanese guidelines, the diagnosis of iNPH relies on a combination of brain imaging and clinical features, with history taking also contributing to the diagnosis (Figure 2).^{55,56} However, in practice, iNPH patients have often sought therapeutic help from multiple specialists (psychiatry, urology, and internal medicine) due to the diversity of clinical symptoms and the difficulty of differential diagnosis from other neurological disorders. Therefore, how to effectively improve the efficiency of early diagnosis and treatment of iNPH is still one of the hot research topics. Perhaps an improved diagnostic approach based on the glymphatic system would be a useful approach.

Clinical Manifestation

It is vital to focus on the clinical manifestations before making a definite diagnosis of iNPH. Therefore, patients

who are clinically compatible with iNPH should be included for further imaging or glymphatic function testing. However, we cannot exclude the effect of glymphatic dysfunction on the clinical presentation and imaging of iNPH, despite there being no more data to support the association. Several studies have reported that intracranial disorders of the glymphatic system may result in loss of homeostasis of the neuronal environment, which may contribute to neuronal malfunction and compression of parts of the cerebral cortex.^{28,57,58} In the case of iNPH, disorders of the glymphatic system caused by different factors can create ventricular dilation and even cerebral white matter lesions, thereby further producing a triad typically characterized by cognitive impairment, urinary incontinence, and gait and balance disorders. It is worth noting that gait and balance disorders are the main clinical manifestations of iNPH patients, while cognitive impairment and urinary incontinence occur as the disease progresses.⁵⁹

Gait and Balance Disorders

Gait impairment in iNPH is best characterized as a higher-level gait disorder. It involves difficulty integrating sensory information about the body's position in its environment in the absence of primary sensorimotor deficits, cerebellar dysfunction, or involuntary movements.⁶⁰ It also includes the effects of gravity, and correctly selecting and executing movement plans for gait or postural reflexes.⁶⁰ These are demonstrated by retropulsion or anteropulsion of stance, hesitation or failure to initiate gait, shuffling and wide-based gait, reduced foot clearance, and difficulty with turning.^{55,56,61,62} Selge et al, (2018) and Nikaido et al, (2018) found that patients with iNPH have a 60–80% probability of falling due to gait and balance disorders.^{62–64} Parkinson's disease (PD), myasthenia gravis, and osteoarthritis (diseases that can also be caused by intracerebral glymphatic system dysfunction), can also cause gait disorders and thus they should be excluded during the diagnostic process. Assessment methods for gait and balance disorders, include but not limited to: timed Up and Go, 10-meter walk test, Functional Gait Assessment, and Berg Balance Scale.^{65–68}

Cognitive Impairment

The cognitive impairment in iNPH patients manifests as frontal-to-subcortical dementia characterized by executive dysfunction, psychomotor slowing, and mood symptoms, especially apathy.^{56,69,70} Approximately 78–98% of patients with iNPH have cognitive impairment, with the

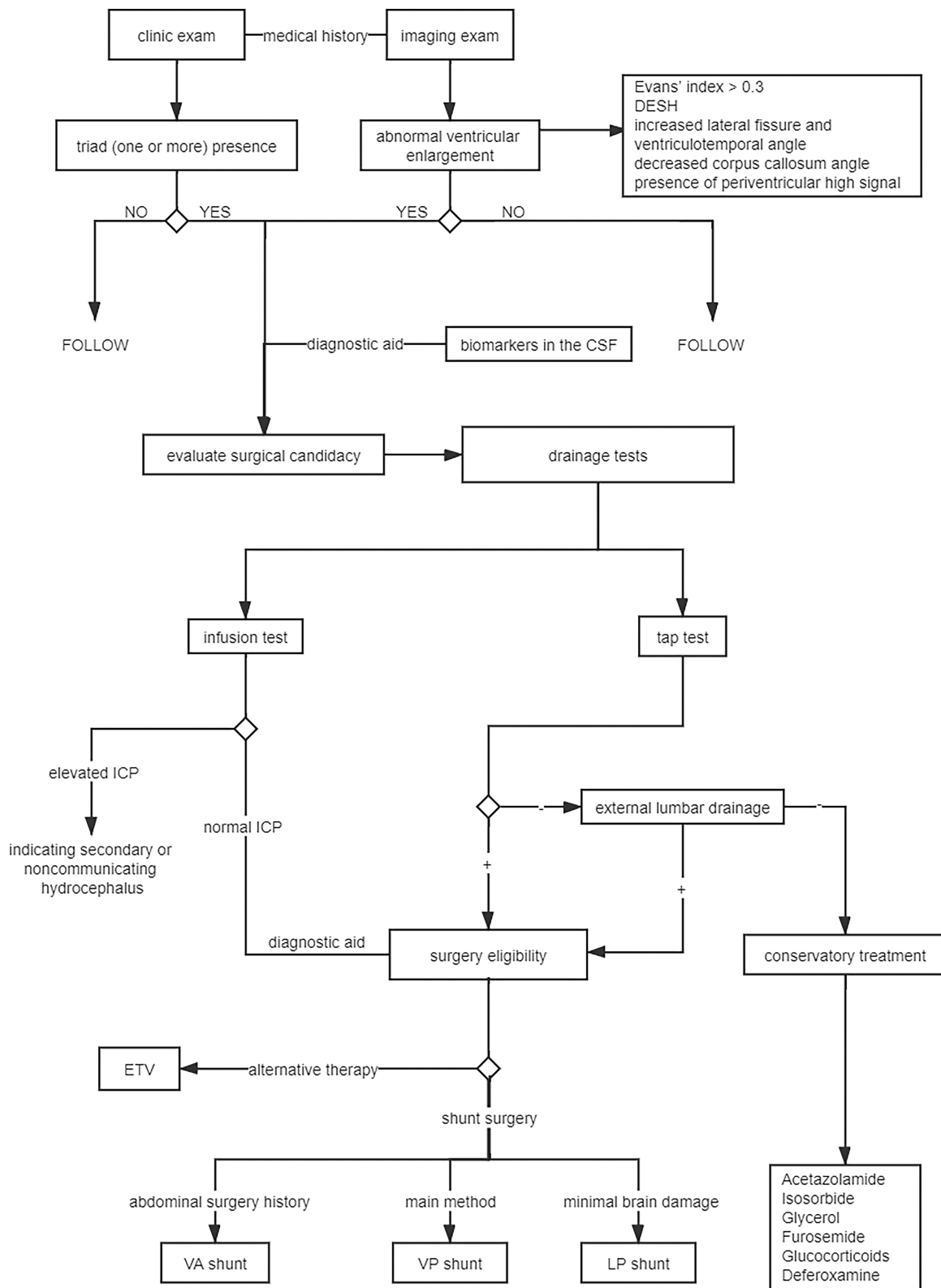


Figure 2 Flowchart for diagnosis and treatment of iNPH patients. The clinical diagnosis of a patient with at least one of the triad of symptoms, together with the imaging diagnosis of abnormal ventricular enlargement, can raise suspicion of iNPH. Medical history and cerebrospinal fluid biomarkers can also assist in the diagnosis. A positive TT can indicate that the patient is eligible for surgery, while a negative TT indicates that the patient requires further testing through an ELD. On the other hand, a positive ELD also indicates that the patient is eligible for surgery, while a negative ELD indicates that the patient requires conservative treatment. In addition, infusion testing can assist in measuring the intracranial pressure to determine the eligibility for surgery. Surgery is most often performed using shunt surgery, and ETV is an alternative surgical therapy.
Abbreviations: CSF, cerebrospinal fluid; DESH, disproportionately enlarged subarachnoid-space hydrocephalus; ELD, external lumbar drainage; ETV, endoscopic third ventriculostomy; ICP, intracranial pressure; LP shunt, lumboperitoneal shunt; TT, tap test; VA shunt, ventricular atrial shunt; VP shunt, ventriculoperitoneal shunt.

degree varying from mild cognitive impairment to dementia.⁵⁵ During clinical diagnosis, frontal assessment battery,⁷¹ the Mini-Mental State Examination,⁷² and Montreal cognitive assessment⁷³ are often used to assess the cognitive function of patients. In practice, Lewy body dementia, PD, and corticobasal syndrome can also produce cognitive dysfunction similar to iNPH. Therefore, the diagnosis should be identified using a combination of neuropsychological examination and fluid drainage tests that can affect the intracranial glymphatic system.⁶⁹ Care also needs to be taken to exclude the effects of schizophrenia, which can have a significant negative impact on cognition, and the inability to obtain a valid evaluation of cognitive function.^{55,56}

Urinary Incontinence

Approximately 76–83% of patients with iNPH typically present with urinary incontinence characterized by urgency and difficulty, which inhibits bladder emptying.^{55,74} Urinary incontinence due to involuntary urination may represent the presence of other comorbidities, and thus the patient's urinary function requires a thorough examination to rule out other neurogenic or urologic disorders, including but not limited to prostate disease and bladder dysfunction.

Drainage Test

Diseases caused by dysfunction of the glymphatic system can also be diagnosed by interfering with the abnormal glymphatic system and observing changes in the clinical presentation. Drainage tests are the most commonly used test for patients with suspected iNPH,^{56,75} with the tap test (TT), external lumbar drainage (ELD), and infusion testing being the three commonly used tests.

Tap Test

Tap test (TT) involves performing a standard lumbar puncture to remove a large volume of CSF from the lumbar CSF space, which is also associated with the glymphatic system.⁵⁵ The reliability of shunt surgery is often estimated by comparing the gait assessment before and after TT because of the better improvement of gait disorder by shunt surgery, and the assessment process can yield good results with or without the aid of equipment.^{76,77} Most importantly, a sufficient volume of CSF needs to be drained to have an effect on the glymphatic system function, which can improve symptoms over time, in order to better assess the shunt effect.^{56,59} Gait is usually

reassessed 30 min to 4 h after the test, and there is also an assessment of urinary and cognitive function after one week in clinical trials.^{71,78} In addition, TT can also be used to distinguish between normal aging-induced and iNPH-induced cerebral deep vein dysfunction, due to the fact that the latter can be rectified in iNPH patients after TT, whereas normal aging cannot.⁵² A previous study reported that the duration of the disease is also a factor, and early detection in the course of the disease yields a high degree of accuracy.⁷⁹ Furthermore, a recent study found that the use of TT to assess the applause sign can effectively delineate the subtype of frontosubcortical disorders in iNPH patients.⁸⁰ The positive predictive value (PPV), negative predictive value (NPV), and accuracy of TT for a favorable response to shunting are approximately 73–100%, 16–42%, and 45–54%, respectively.^{55,81}

External Lumbar Drainage

External lumbar drainage (ELD) requires the patient to be hospitalized and undergo continuous CSF drainage, often performed when symptoms do not improve after TT and iNPH is still suspected.⁸¹ Briefly, a tuohy needle is inserted and CSF is drained at a slower rate for long periods of time in large volumes (10–14mL/h for about 72 h).^{55,56} Moreover, gait evaluation is still required after drainage. ELD is a more reliable method for predicting shunt response in iNPH than TT, with its PPV, NPV, and accuracy values being approximately 1–100%, 36–100%, and 58–100%, respectively.⁸¹ However, it requires a more specialized physician to perform, and is not the preferred clinical choice due to its complexity and the potential for infection from prolonged drainage.

Infusion Test

The infusion test is a “quick, easy, and handy” diagnostic protocol which determines the CSF outflow resistance or CSF conductance. However, it is less commonly used worldwide, and is only common in Europe. Briefly, two lumbar puncture needles are inserted into the lumbar subarachnoid space: the first needle is connected to an infusion pump to infuse artificial CSF, while the second needle is connected to a closed-pressure recording device.⁸² Previous studies have reported that the inclusion of CSF outflow resistance values in the selection of patients undergoing shunt surgery has been associated with a significant improvement in postoperative patient outcomes.^{83,84} The test also requires specialized physicians and specialized

equipment to perform, and has a PPV of approximately 75–92%.⁵⁵

Biomarkers in the Glymphatic System

iNPH is a multifactorial disease with a high number of neuropathological changes, which in turn result in changes in the composition of the glymphatic system such as CSF, despite the absence of specific signs. CSF protein biomarkers reflect fundamental pathological changes occurring in the CNS and the changes may have positive implications for the pathophysiology of iNPH pathogenesis.⁸⁵ Therefore, these changes are of great significance for the early diagnosis of iNPH because they partially trend in the early stages of the disease. However, they need to be differentiated from other neurological diseases and thus more research is required to explore them.

Schirizzi et al, (2018) found that the markers of subcortical damage (neurofilament light, myelin basic protein, and leucine-rich- α 2-glycoprotein) were increased in iNPH patients.⁸⁵ Other significant findings included the reduction of all amyloid-beta-related proteins, either soluble amyloid precursor proteins or A β fragments (A β 42, A β 38, and A β 40), together with the mild lowering of tau proteins (total tau and phosphorylated tau).^{85–87} In combination with these findings, elevated monocyte chemoattractant protein 1 was shown to separate patients with iNPH from healthy individuals and patients with vascular dementia, PD, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, AD, frontotemporal lobe degeneration, and other cognitive and movement disorders with a good diagnostic sensitivity and specificity.⁸⁸ The A β 42/A β 40 ratio also contributes to the differential diagnosis of iNPH with AD and other dementias, but shows poor associations with clinical variables.⁸⁹

Although CSF biomarkers have been studied extensively, the study of CSF biomarkers in iNPH is relatively new. Thus, iNPH-specific CSF biomarkers with strong evidence have not yet been identified, and there is no proven or substantiated role in diagnosing iNPH. However, research methods continue to innovate and provide new ideas for the exploration of CSF biomarkers and the diagnosis of iNPH such as two-point CSF collection and observing dynamic changes in CSF biomarkers,⁹⁰ which is providing new ideas for auxiliary diagnostics.

Radiological Examination

Currently, the connection between imaging and the glymphatic system has not been precisely defined, although

many researchers have attempted to visualize the function and structure of the glymphatic system in vivo using MRI.⁹¹ Several scientists have used the “Diffusion Tensor Image-Analysis along the Perivascular Space” method to examine iNPH patients. It has been found to be a useful imaging tool for identifying glymphatic dysfunction and for individually quantifying the glymphatic activity in iNPH patients.^{92,93} Disorders of the glymphatic system in the brain can affect different parts of the brain, thereby manifesting different diseases, some of which can be distinguished by neuroimaging. For example, a previous study reported that diffusion tensor imaging provides a quantitative measure of neurological fractional anisotropy (FA).⁹⁴ FA decreases in general neurological diseases but increases in the corticospinal tract in iNPH patients, a phenomenon that distinguishes iNPH from other neurological diseases such as AD and PD.^{94–96}

In addition, visualization of brain lesions can be represented by imaging and is an important diagnostic modality in tradition. The most common diagnostic imaging marker in iNPH patients is the abnormal enlargement of the ventricles. Patients with iNPH present with abnormally enlarged ventricles without CSF flow disorders, but those with enlarged ventricles do not necessarily have iNPH.⁵⁶ The main indicators for evaluating ventricular enlargement are Evans’ index, callosal angle, the size of temporal horns, narrow high-convexity sulci, dilated Sylvian fissures, focally dilated sulci, periventricular hypodensities, and bulging of the lateral ventricular roof.^{1,97,98} Evans’ index, the ratio of the widest frontal horn span to the widest diameter of the brain on the same axial image, is a more frequently used test. However, both the imaging angle and the layer affect the EI value, and the value is age-dependent. Patients with iNPH exhibit a positive Evans’ index (>0.3),^{99–101} but it is not specific for patients with brain atrophy due to other factors such as AD.¹⁰⁰ A recent study presented a new method for assessing the anteroposterior diameter of the lateral ventricle index (>0.50), which can distinguish iNPH patients and age-matched elderly subjects with healthy Evans’ index.¹⁰²

Some other imaging manifestations may also help in the diagnosis of iNPH such as disproportionately enlarged subarachnoid-space hydrocephalus (DESH), which is also a form of glymphatic dysfunction.¹⁰³ Several studies have shown a good correlation between iNPH and DESH signs,^{39,103–105} and the combination of DESH features measured using voxel-based morphometry and the Evans’ index can distinguish iNPH, AD, and normal

aging.¹⁰⁶ However, Takagi et al, (2020) reported that the Evans' index >3.0 and DESH lead to a 70% misdiagnosis rate when both are included in the diagnostic criteria for iNPH.¹⁰⁷ Therefore, DESH is not yet specific for judging whether a patient has iNPH, and it is still highly controversial in the available studies.

Glymphatic System and Treatment of iNPH

In general, iNPH is a progressive neurological disorder, and glymphatic disorders can continue to cause damage to the brain if left untreated.¹⁰⁸ Therefore, patients generally undergo surgery as soon as possible after the diagnosis of iNPH, including Ventriculoperitoneal shunt (VP shunt), Ventricular atrial shunt (VA shunt) and Lumboperitoneal shunt (LP shunt), and alternative surgery such as endoscopic third ventriculostomy (ETV). The appropriate surgical treatment is often decided based on the patient's specific clinical assessment and medical history. Isik et al, (2019) reported that the deterioration of gait disturbance may be improved, and cognitive decline may be stabilized by applying recurrent CSF removal.⁶⁸ However, patients who are not candidates for surgery will be treated medically and conservatively due to the complications of shunt surgery, and the patient's age and physical condition (Figure 2).

Conservative Treatment

Conservative treatment is often symptomatic and based on the patient's clinical presentation, and it alleviates the patient's temporary symptoms which cannot be thoroughly cured. A previous study proposed acetazolamide, a carbonic anhydrase inhibitor, as an alternative to shunting for adults with NPH in order to address glymphatic dysfunction in the brain.¹⁰⁹ The choroid plexus contains high levels of carbonic anhydrase and acetazolamide effectively inhibits the production of choroid plexus CSF. In addition, acetazolamide has been shown to inhibit aquaporin-mediated water conductance through several molecular pathways.¹¹⁰ In addition, Alperin et al, (2014) reported that administration of oral acetazolamide is associated with a decrease in the periventricular hyperintensities observed through MRI.¹¹¹ Other drugs including isosorbide, glycerol, furosemide, glucocorticoids, and deferoxamine, can also be used for conservative treatment of hydrocephalus,¹¹² but no corresponding studies are available for iNPH treatment.

Shunt Surgery

According to clinical guidelines, early shunt surgery is still recommended for patients with iNPH to improve intracranial glymphatic dysfunction.¹¹ The indication for surgery is determined using the sum of clinical symptom data (complete or incomplete triad), hydrocephalus images obtained by MRI or CT, and test results (a positive test result is an absolute indication for surgical treatment).¹¹³ A shunt system is comprised of three connected parts: a proximal catheter which may be placed in the lateral ventricle or lumbar cistern; a distal catheter which is placed in an absorptive cavity such as the peritoneum or the atrium of the heart; and a valve which connects the proximal and distal catheters to help regulate the rate of CSF drainage.⁵⁵ Some studies found that the CSF biomarkers were altered after undergoing shunt surgery, suggesting that shunt surgery may improve glymphatic system dysfunction.¹¹⁴

Ventriculoperitoneal Shunt

The current standard treatment for iNPH involves the implantation of a ventriculoperitoneal (VP) shunt.¹¹⁵ Several studies have demonstrated improvements in cognition, gait, and urinary function in iNPH patients after VP shunt;^{75,116} with an average improvement of approximately 71%.¹¹⁷ Glymphatic factors that predicted a positive outcome with VP shunt include higher CSF outflow resistance, a positive response to an ELD or TT, and a positive reduction in cerebral blood flow with the use of acetazolamide.⁷⁵ On the other hand, the factors that predicted a negative outcome included higher age and previous cerebrovascular disease.¹¹⁸ Common early complications of the surgery include infection, subdural hematoma and subdural fluid, and occurrence of occasional excessive drainage.¹¹⁹ However, the improvements in shunt technology and shunt devices such as the use of anti-siphon devices and the selection of shunt valve pressure have resulted in the complications being avoided. Farahmand et al, (2016) reported that there is no clinically significant difference between using 40 mmH₂O and 200 mmH₂O in shunt valve pressure.¹²⁰ Moreover, a personalized dynamic pressure strategy can be developed based on the patient's clinical manifestations, imaging results, and changes in the drainage test. The use of an adjustable valve gate can effectively aid in the realization of this protocol.¹²¹

Ventricular Atrial Shunt

Ventricular atrial shunt (VA) shunt is the main treatment option for the patients who are not suitable for VP shunt

due to some abdominal factors¹²² such as ascites, overweight, or history of abdominal surgery.^{123,124} Nunoo-Mensah et al, (2009) reported that approximately 43.8% of the patients over the age of 65 have undergone abdominal surgery.¹²⁵ Previous studies have also reported that there is no significant difference in gait improvement between patients who underwent VA shunt and those that underwent VP shunt, and the overall incidence of post-operative complications (infection and shunt obstruction) is similar in both groups.^{12,126} Subdural hematoma is the most common complication in patients after VA and VP shunt, but Mcgovern et al, (2014) reported that its incidence is significantly higher after VA shunt than after VP shunt.¹²⁶ In addition, VA shunt may cause cardiopulmonary complications such as endocarditis and pulmonary heart disease, thereby leading to increased post-morbid mortality.¹² Thus, VA shunt surgery is often an alternative treatment method despite being an effective modality for the treatment of iNPH. Therefore, VA shunt may be more widely used if a safe and favorable condition is provided.

Lumboperitoneal Shunt

Lumboperitoneal (LP) shunt is a minimally invasive procedure which does not cause direct trauma to the brain, thereby avoiding the development of hematomas in the brain parenchyma.³⁴ A study comparing LP and VP shunts found that both improved symptoms in patients with possible INPH, with no significant difference in outcomes between the two methods,¹¹⁵ and no significant difference in the incidence of postoperative complications.¹²⁷ In Japan, LP shunt is used for the treatment of iNPH in a larger number of patients despite not being widely used internationally.¹²⁸ This is because it is the least invasive treatment method and it causes the least damage to the brain.

In addition to the above mentioned three types of shunts, we also have ventriculopleural shunt, retrograde ventriculosinus shunt,¹²⁹ and ventriculogallbladder shunt,⁵⁷ but there is a lack of strong data to prove their safety and efficacy. Moreover, there are currently no international standards for evaluating the results of various types of surgeries, and the improvement rates of patients after surgery are partially different. In some cases, extra shunt surgery is required when catheters are misplaced or infections occur aggravating disorders of the glymphatic system. A previous study involving a 12-month follow-up survey reported that 14.7% of patients required extra shunt surgery.¹¹⁹

Endoscopic Third Ventriculostomy

Endoscopic third ventriculostomy (ETV) is the use of a neuroendoscope to puncture a hole in the bottom of the third ventricle with the goal of establishing a channel between the ventricular system and the subarachnoid space, which permits CSF to flow into the suprasellar cistern. This approach directly alters the circulatory pathways of the glymphatic system and, in clinical trials, its overall benefits outweigh the disadvantages. Moreover, ETV is also a promising treatment option for iNPH in cases where there is evidence of narrowing of the fourth ventricular outflow tract catheter.^{130,131} ETV is mostly used to treat obstructive hydrocephalus, but many trials have started using it to treat iNPH.^{132,133} The average success rate of ETV for the treatment of iNPH is reported to be as high as 63%, but more than 50% of patients require revision surgery after ETV. Therefore, it is not the primary treatment method for patients with iNPH and there is no proven or substantiated role.¹²¹

Conclusions and Prospective

iNPH is one of the few neurodegenerative diseases that can be treated successfully, but, in reality, it is still a severe disease in many patients. Physicians make a variety of diagnoses based on clinical guidelines due to the variability of patients' conditions. Nevertheless, misdiagnosis and omission still occur, which leads to further deterioration of patients. In-depth investigation of the links between the glymphatic system and the pathogenesis of iNPH can optimize the current diagnostic approaches and prevent early aggravation of the disease. Furthermore, studies can identify the characteristics of the disease with a high degree of correlation by targeting the differential expression of neuroimaging and CSF biomarkers in patients with iNPH. A separate exploration of each component is not sufficient for gaining a deep understanding of iNPH, and thus combining the components and setting up different weighted scales may be more helpful in the diagnosis of iNPH. In response to the increased glymphatic volume in the brain, iNPH patients are often advised to undergo shunt surgery as soon as possible after diagnosis. The adjustable-valve gate in shunt surgery reduces the incidence of post-shunt complications, thereby resulting in a better prognosis for patients after one year. However, the prognosis gets worse over time. ETV can also be widely-used as a therapeutic means of treating iNPH if more robust studies demonstrate the

effectiveness of ETV in iNPH patients. In addition, recurrent CSF removal may be an alternative treatment approach for the patients who are not candidates for surgery. However, further studies should be conducted in the future to determine the factors influencing positive and negative shunt results, as well as diagnostic screening and improvement of shunt and ETV in patients with iNPH, with the overarching goal of giving superior outcomes for iNPH patients.

Abbreviations

A β , amyloid β ; AD, Alzheimer's disease; AQP, aquaporin; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; DESH, disproportionately enlarged subarachnoid-space hydrocephalus; ELD, external lumbar drainage; ETV, endoscopic third ventriculostomy; FA, fractional anisotropy; ICP, intracranial pressure; iNPH, idiopathic normal pressure hydrocephalus; LP shunt, lumboperitoneal shunt; MRI, magnetic resonance imaging; NPH, normal pressure hydrocephalus; NPV, negative predictive value; PD, Parkinson's disease; PPV, positive predictive value; TT, tap test; VA shunt, ventricular atrial shunt; VP shunt, ventriculoperitoneal shunt.

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Disclosure

The authors report no conflicts of interest in this work.

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